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and

The Environmental Sciences

Research and Training in Toxicology for FY 1980 and Beyond

Interagency Regulatory Liaison Group

November 1978

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Preface

This report is an attempt to overcome self-interest. For the first time, it sets out a proposal for a national effort in toxicology related to human health that is not bound by individual agnecy interests. As such, the ideas and priorities expressed here do not necessarily reflect the precise views of diverse agencies--each with somewhat different missions. Rather, the paper raises for discussion and debate issues that have simmered for too long at the technical level. If it serves as the catalyst for settling on priorities in an important area of health protection, it will have served its purpose.

It is always easier to debate our next moves, rather than to look hard at what we are already doing. Fortunately, the Executive Office of the President, Office of Management and Budget, elected to undertake a comprehensive zero-based review of toxics research in the summer of 1978, as this paper was being prepared. The results of that review should be available in early 1979. Consequently, this report--in the interest of time--addresses only the future. This paper does, however, reflect the budget figures used in the OMB analysis, with qualifications where they are thought to be necessary.

Important questions of management are also not discussed. In the fall of 1978, the Department of Health, Education, and Welfare announced the establishment of a National Toxicology Program to deal primarily with testing and test development. New management mechanisms were announced by HEW, and these and other ideas are currently under study by the other affected agencies.

In large measure, the paper uses the Report of the Second Task Force for Research Planning in Environmental Health Science, Human Health and the Environment-Some Research Needs, as a base. The interested reader should look to this 1977 HEW publication for a fuller explication of the specific research projects that must be done.

Special thanks go to Ms. Mary Cottone of FDA, and Mr. Earl Steinberg of Harvard University, Kennedy School of Politics for their help in preparing this report.

Table of Contents

A. Introduction--Prevention and the Toxics Revolution 1
B. Scope of this Paper 3
C. The Extent of the Problems 4

1. Reproductive and Developmental Toxicity
2. Mutagenesis 5
3. Carcinogenesis 6
4. Degenerative Diseases 7
5. Neurological and Behavioral Toxicology 11
6. Environmentally Induced Immunologic Disease 12

D. Categorizing the Functional Scientific Components of Solutions 13

1. Exposure Analysis 14
2. Laboratory Research
3. Clinical and Epidemiology Approaches 17
4. Risk Assessment 19

E. The Necessity for Choice: Some Criteria for Scientific Action 20

1. Reproductive and Developmental Toxicity 21

A. The Existing Data Base
B. The Ability to do Further Analysis 22
C. Likelihood of Near-Term Payoff
D. Ranking the Importance of Functional Work 23

2. Mutagenesis
3. Carcinogenesis 24
4. Chronic Degenerative Disease 27
5. Neurotoxicity and Behavior 29
6. Immunologic Disease 30
7. Summarizing the Scientific Criteria 32

F. Targeting for Action: The Social Problem 34

1. Objective 35
2. Criteria for Choice

A. The Concept of Marginality
B. Long-run vs. Short-term: Individual vs. Species
C. Transferring Knowledge of Action - Regulatory Importance 37

3. Ranking the Problems

G. The Problem of Training 38

1. Demand in the Discipline 39
2. Program Requirements
3. Who benefits?
4. Establishing a Priority 40

H. Policy Alternatives

I. How Much Should We Spend? 44

1. Problems with the Base
2. Conclusions 46
3. Cost Estimates 47

Table of Funds

Appendix 1 -- Task Force

Executive Summary

Preventive Health and the Environmental Sciences

I. Introduction

The quality of life and the state of our people's health must be protected and improved by preventive health efforts. People cannot reduce all risks through voluntary action. Government has an obligation to make sure that people are protected from involuntary health risks and to prevent health problems before they occur. That is the major purpose of health regulation and of the research enterprise associated with it.

To meet the challenges of environmental health, we propose alternative directions and recommendations for new efforts in Government toxicology. This paper identifies the major health problems related to toxic substances in the environment and describes the kind of knowledge necessary to combat these problems successfully. It then discusses various objectives to which the Government might reasonably aspire and develops criteria for choosing actions to achieve them. It constructs alternative reasearch and training packages and makes cost estimates.

The paper was developed by a task force sponsored by the Interagency Regulatory Liaison Group (IRLG), an alliance of the Consumer Product Safety Commission, the Environmental Protection Agency, the Food and Drug Administration, and the Occupational Safety and Health Administration. Task Force recommendations were then subject to interagency review. This paper reflects the results of that review as well as the views of the individual task force members.

II. The Extent and Importance of the Health Problems

Environmental toxins are known to contribute to six important health problems:

1) Reproductive and developmental toxicity;

2) Mutagenesis (particularly chromosomal mutation and single dominant gene mutation);

3) Carcinogenesis;

4) Chronic degenerative diseases (including arteriosclerosis, ischemic heart disease and other cardiac conditions, hypertension, emphysema, and others);

5) Neurological and behavioral toxicity; and

6) Environmentally induced immunologic diseases.

Defining the scope of the problems in these areas is difficult, inasmuch as some involve conditions that may not manifest themselves as disease in the population for some time.

Responsible public policy demands not only the identification of "health problem targets" for research, but also some ranking among them to guide the allocation of resources. We developed the following criteria for ranking the disease problems for new action--in addition to a subjective evaluation about the general seriousness of the disease problem.

1) The expected effect of research--based on what is currently known about the problem as well as taking into account of the past and present investment.

2) An emphasis on present (short-term, individually oriented) problems over species oriented, long-run problems--although some emphasis must surely be given to problems that have long-term consequences for the species.

3) An emphasis on areas that seem to be of greatest regulatory importance.

We applied these criteria to the various disease problems and came to the following conclusions:

1) Methods for identifying and controlling environmental causes of chronic degenerative diseases, such as emphysema, diabetes, renal, and cardiovascular diseases, need to be the top priority for efforts in the near-term future.

2) Although emphasis on cancer research per se has quadrupled in the past decade, the problems of environmental carcinogenesis are so large--both in terms of social costs and the requirements of

regulation--that the area must still be given high, though not the highest, priority. We cannot discount the psychological costs of suffering and fear that derive from this complex of diseases. It may be time for a reordering of priorities in the environmental carcinogenesis area so that more work is devoted to identifying less hazardous alternatives to carcinogenic substances.

3) Reproductive disorders and birth defects must take on new importance in light of the state of the art, and the possible magnitude of these problems. In the long run, the costs imposed by this area may be the most important to remedy.

4) The problems of neurotoxicity, mutagenic disease and immunologic disease all deserve increased attention as their prevalence becomes known; but research here can be expanded at a somewhat slower pace.

III. Ranking the "Functional" or "Support" Areas of Research

We examined four general areas in which research must be conducted to have an impact on these health problems:

1) Exposure analysis (including sampling, analytic and predictive methods, as well as methods to measure the total exposure and body burden of chemicals);

2) Laboratory research (including short-term test development, development of model ecosystems, definition of interactions between hazardous substances, development of early indicators of toxicity and more predictive animal models);

3) Clinical research (including test methods to identify individuals or population groups being exposed to high risk from toxic hazards, as well as traditional epidemiology);

4) Risk assessment research (to meet ultimate regulatory needs).

Using the criteria of "researchability", i.e.

1) The strength of the existing data base upon which to build;

2) The ability to do further analysis and experimentation (the "state of the art"); and

3) The size and likelihood of payoff, as well as an assessment of opportunity cost.

we investigated each "support" area under every disease category, and reached the following conclusions:

1) Laboratory research is still the most critical area overall, although clinical indicators of toxicity and epidemiology are considered most important in the area of chronic degenerative disease.

2) Clinical indicators of toxicity, including epidemiology and exposure analysis rank very closely behind laboratory problems overall.

3) As we make progress on the clinical, laboratory and exposure fronts, we will need to shift emphasis toward risk assessment. At this time, however, it would be premature to make risk assessment research the highest priority, even though risk assessment per se must obviously be done right now.

We also believe that more research should be directed at identification of production technologies that pose less significant health hazards. Investment in this area could produce a more rational approach to the adoption of safer technologies and prevent costly technological shifts that result from inadequately researched regulatory initiatives.

IV. The Problem of Training

The benefits of any research effort will not be fully realized unless an adequate research work force is present. We recommend consideration of a new program designed to cross-train people in disciplines other than their primary discipline (like microbiology and analytic chemistry) in toxicology. We do not believe that a large investment needs to be made in training new graduate students in toxicology per se. It is important to begin this training immediately. However, we assume that half of the total necessary support should be supplied by the private sector, and that the current ability of toxicology and epidemiology training facilities are limited. As a result, we believe that fewer funds need to be allocated for training than other research areas.

V. Policy Alternatives

We described four reasonable alternatives based on this previous analysis:

1) Target new research and training at the most important disease problems;

2) Target new research and training monies on the most important scientific problems, primarily using the "researchability" criteria;

3) Orient all new research and training toward regulatory needs;

4) Target resources in a way that balances health endpoints, regulatory needs, and the scientific capability of the research enterprise.

We recommend alternative four.

VI. How Much Is Enough?

After a brief examination of current spending on toxicology research (including an examination of all existing data bases and the deficiencies among them) related to human health, we concluded that:

1) The total level of current spending on human health efforts is about $500 million.

2) No reliable data base exists with which everyone agrees, although both the Council of Environmental Quality and the OMB have recently diminished the uncertainty substantially.

3) No large scale duplication or overlap exists between research done by research and regulatory agencies.

4) More research needs have been identified than can be funded with available near-term resources.

Table 1 shows how we would allocate $200 million in new resources among the various problem areas if funds become available. In essence, this table quantitatively demonstrates our priorities.

Table 1

Allocation of Funds

	"Functional" Research and Training Categories						
	Lab Techniques[1]	Clinical[2]	Exposure[3] Analysis	Risk Assess-ment	Training	Other[4]	Total
Disease Category							
1. Chronic Degenerative Disease	$12.5[5]	$17.5	$10	$5	$4	0	$49
2. Environmental Cancer	8	4	12	2	2	12	40
3. Reproductive Toxicity	12	8	8	8	3	0	39
4. Neurotoxicity and Behavior	9	9	6	3	3	0	30
5. Mutagenic Disease	4	6	8	2	2	0	22
6. Immunologic Disease	6	4	4	4	2	0	20
Total	$51.5 Million	$48.5 Million	$48	$24	$16	$12	$200

1. This includes short-term test development, development ecosystems, interactions between hazardous substances, early indicators of toxicity, and more predictive animal models.

2. Includes epidemiology.

3. Exposure analysis includes sampling and analytic methods, methods to measure total exposure, and body burden of chemicals.

4. Development of alternative technologies to reduce cancer risk.

5. All numbers are expressed in millions of dollars.

Preventive Health and the Environmental Sciences

A. Introduction--Prevention and the Toxics Revolution

The quality of life and the state of our people's health must be protected and enhanced by preventive health efforts.

The signs of public acceptance of this view are clear: more serious interest in nutrition, concern about smoking, emphasis on recreational exercise. If pursued voluntarily by our citizens, these initiatives can generate great health benefits at lower cost than expenditures on curative medical technology.

This encouraging movement derives in part from other changes in the national attitude. In the past ten years, we have come to recognize the meaning of limits: limits on our capacity to decide for others, limits on the value of technology, limits on the capacity of our environment to support all uses we would like to make of it. Part of the recognition has been a growing sense that Government cannot accomplish everything, that individuals must do more for themselves. America's increasing health consciousness is stimulating people to assert themselves and take control of their own lives.

The challenge for Government is to facilitate this process in as unobtrusive a manner as possible. The proper governmental role should often be limited to encouragement, to the provision of information, education, or facilities or to the creation of environment in which individual initiative may succeed.

People cannot reduce all risks through voluntary action, however. Government does have some obligation to ensure that the agricultural and industrial developments from which our society benefits do not present our citizens with unreasonable health risks. That is the major purpose of health regulation and the research enterprise associated with it.

A large part of the environmental health problem derives from the remarkable revolution in synthetic chemistry which has been taking place in the United States and other developed nations since World War II. This scientific explosion has produced all the commonly-used varieties of pesticides, and many other agricultural chemicals and a wide range of industrial chemicals. In many ways these chemicals are similar to those in living systems, so it is not surprising that they are sometimes active

against life; cancer, birth defects, and various chronic diseases--especially in the elderly--have been associated with exposures to synthetic chemicals in the work place, the environment, and in the food supply. Congress has recognized the significance of these hazards, and has taken important legislative steps to protect the American people from them. The Occupational Safety and Health Act, the Consumer Product Safety Act, The Food, Drug, and Cosmetic Act, the National Cancer Act, and most recently the Toxic Substances Control Act all attempt to deal with this problem.

The risks posed by chronic exposure to hazardous chemicals extend to the future as well as present generation. Americans now reaching age 65, and entering their period of greatest vulnerability to such chronic afflictions as heart disease, cancer, and stroke, have been exposed to the "new" chemical environment for about 25 years--only about two-fifths of their lifetime. We must worry even more about the millions of Americans who are 25 and under--born after the new environment was established. They will not reach age 65 until the year 2018 or after; but they will have had a lifetime of chemical exposure. We know that the likelihood of developing cancer as a result of chemical exposure increases with the duration of the exposure--not simply in a straight line, but at an accelerating rate--so that 20 years of exposure is much more than twice as dangerous as ten. We cannot afford to wait to take action until after disease problems of tremendous magnitude are upon us.

Now is the time to commit ourselves to understanding and reducing the health risks imposed by the environment. Now is the time to prevent the diseases of the next generation, and to invigorate and support the actions of our citizenry.

This is no plea for a return to the pristine wilderness, nor does it envision the imposition of heavy costs upon the taxpayers of our country. Rather, we argue that the understanding and reduction of environmental health problems is crucial to the achievement of our national objectives. Our national research capability is such that it can be used effectively to develop safer technologies for the future health of the American people. If Government does not concern itself with environmental health risks, the preventive health movement will be endangered, because individual action will often fail to bring about desired results.

B. Scope of this Paper

To meet the challenge of environmental toxins, this paper proposes a new direction for American science and technology. It identifies in general the major human health problems caused by environmental toxins, as we now know them, and identifies their societal costs, when possible. It goes on to describe the kinds of knowledge necessary to combat these problems effectively. It then presents an objective to which the Government might reasonably aspire in both the short and long run and develops criteria for choosing actions to achieve it. It also constructs alternative research and training packages capable of meeting those objectives. A final set of recommendations is made.

This paper emphasizes toxic substances because of our belief that increased knowledge about them will most quickly guide government action to limit their use. The paper emphasizes science, rather than immediate action programs, because rational action requires a level of knowledge that does not now always exist. Other governmental "prevention" programs are underway dealing with substances such as tobacco and alcohol, whose health risks are more clearly defined.

This paper was developed by a task force sponsored by the Interagency Regulatory Liaison Group (IRLG). This group is an alliance of the Consumer Product Safety Commission, the Environmental Protection Agency, the Food and Drug Administration, and the Occupational Safety and Health Administration.

This entire effort builds upon the detailed work the Second Task Force for Research Planning in Environmental Health Science. Interested technical readers are referred to this work.[1]

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1 Human Health and the Environment--Some Research Needs, Report of the Second Task Force for Research Planning in Environmental Health Science, U.S. Department of Health, Education, and Welfare, PHS, NIH, NIEHS, DHEW Publication No. NIH 77-1277.

C. The Extent of the Problems

In this section, we identify the major health problems resulting from environmental stresses, and try to provide some perspective on what is known about them. To the extent that health care costs are known, we provide them, as well as an assessment of our current ability to detect the problems and, the reliability of the information used to act upon the problems.

1. Reproductive and Developmental Toxicity

Successful reproduction and development are obviously critical to the survival of all organisms.

More chemical damage may be done during embryonic development than during any other phase of the human life cycle. Over one third of early embryos die and about 15% of recognized pregnancies abort spontaneously. Among the surviving fetuses, at birth, approximately 3% have developmental defects of form, chemical content or function; with increasing age over 7% (210,000 per annum) show detectable defects.

In 1974, 12.3 infants per 1,000 live births died within 28 days and 16.7 per 1,000 live births died within 1 year. This represents a 35 year decline of about 57% for the early deaths and a 65% decline for children dying before their first birthday. Maternal mortality in the U.S. declined 90% between 1930 and 1960. But our problems are not limited to those that cause death.

Of the hundreds of agents known to be teratogenic in laboratory animals, about 25 are presently known to affect humans; many of the rest are suspected, including:

- Therapeutic radioiodine;
- Rubella virus, cytomegalovirus, herpes virus hominis, Types I and II, varicella virus, Venezuelan equine encephalitis virus;
- Androgenic hormones, aminopterin and methylaminopterin, cyclophosphamide, bisulfan, thalidomide, organic mercury, diethylstilbestrol, coumadin derivatives, diphenylhydantoin.

Other disease conditions, either in the mother or fetus, known to cause teratogenic changes include:

- o toxoplasmosis, syphilis, endemic cretinism, diabetes, phenylketonuria and virilizing tumors.

The risks and effects on reproduction caused by environmental agents are difficult to assess, however, because of the lack of credibility of current lab tests, the complexity of the biological and chemical processes involved and the span of years required for reproductive maturation. Consequently, it is difficult to impute direct costs with accuracy. Mental retardation, however, provides an indicator of the striking cost of birth defects. Nearly $1 billion per year is spent on institutionalized patients who have been retarded since birth; an equal amount is probably spent on non-institutionalized retarded patients. Society pays heavily for these types of defects in terms of decreased quality of life.

2. Mutagenesis

Genetic changes may cause structural anomalies, alterations in the biochemical system or fetal death. Some experts believe that chemical mutagenesis may be involved in as much as 10% of all human disease.

There is currently no known way of estimating the health burden caused by mutagenic chemicals. Three major categories of burden can be identified, however;

- o Chromosomal Mutation, particularly Downs' Syndrome (Mongolism). Approximately 15,000 children per year are born with this syndrome.

- o Single Dominant Gene Mutation

  Over 1,000 dominant gene mutations are known in man. Some of these can induce hereditary neoplasms, e.g., retinoblastoma. 15,000 children per year are affected by structural anomalies and physical malformation. It is impossible to access now how many of these abnormalities might be caused by single dominant gene mutations.

- Recessive Gene Mutation

About 1,000 disorders such as sickle cell anemia and Tay-Sachs disease are expressed if both parents possess and transmit specific recessive genes to an offspring. It is difficult to estimate the total size of the carrier group because the disease goes undetected until two carriers transmit the mutant trait to their offspring.

While a number of test systems can be used to detect single dominant gene and recessive gene mutation at the molecular level, the reliability of the system is controversial. Quantification of risk in this area lags behind that available for, say, carcinogensis. The result is that estimated societal cost is again speculative, but could approach hundreds of millions of dollars.

3. Carcinogenesis

One thousand Americans die each day from cancer. 1,000,000 new cancer cases are reported each year. A large proportion of cancers are related to environmental agents such as ionizing radiation and chemical substances. Exposure of an individual to carcinogenic factors begins with the germ cells of the parents, extends through embryonal and fetal development, and continues from birth to the end of life.

Present evidence indicates significant risk associated with both repeated multiple exposures, and the combined effects of different agents.

Because of the great attention that has been devoted to cancer, we have begun to get some handles on its contol. The control of radiation exposure since the 1940's has undoubtedly prevented a large nunber of cancers. Cessation of smoking prevents the further increase of cancer risk; smoking of filter cigarettes is probably accompanied by a somewhat lower risk of lung cancer.

Selective occupational prevention has reduced the cancer risk of several industrial processes. Much however remains to be done, particulary in light of evidence that cancer death rates seem to increase for certain population groups (e.g., blacks) and for various forms of the "disease," while lung cancer rates continue to rise at a quick pace for the entire population.

Significant problems still exist in trying to categorize the magnitude of the environmentally imposed cancer risk. Epidemiology, early indicators of exposure, screening tests for toxic chemicals, definitive toxicological tests, estimations of dose response, and a host of other techniques need to be perfected before the disease causes are adequately mapped, let alone dealt with.

Even with incomplete information, it is possible to chart the cost of this killer. The direct monetary cost of cancer is currently estimated at $30-35 billion per year. With that as a background, it becomes possible to consider the full economic impact of environmental cancer prevention. Reduction of exposure to or elimination of a source of environmental carcinogens need not place a burden on the economy. Development of safer "alternative" techniques can generate new jobs and new profits; more effective controls in the manufacture or use of certain products can lead to more profitable operations. The relatively small costs of early pre-testing of new products must be compared with the enormous societal costs associated with discovering a health problem after investments in technology have been made and wide damage needs to be "repaired".

4. Degenerative Diseases

There is virtually no current chronic disease to which environmental factors are not contributing, either (a) by direct or indirect action on the organ itself, or (b) through an influence on modulating mechanisms of neuroendocrine or immunologic nature. For every one of the multitude of cardiovascular, pulmonary,

renal, hepatic, pancreatic, gastrointestinal, cutaneous, and neurologic diseases, as well as disorders of the hematopoietic system, examples exist of toxic manifestations brought about by the direct actions of environmental stresses. The influence of these stresses on modulating mechanisms is probably more general, more pervasive and more subtle, yet more likely to be decisive.

Our ability to understand and prevent these diseases is hampered severely because they generally result from a complex interaction of genetic susceptibility, nutritional state, and physical and emotional stresses, in addition to specific exposures to chemical, physical or biologic agents in the environment.

The contribution made by environmental chemicals to the induction of various disease entities is undoubtedly quite varied. In some diseases there is a very strong genetic or nutritional component with relatively little known contribution from environmental toxins. In others the toxic component is very strong. The effectiveness of disease prevention methods is dependent on the feasibility of controlling a contributing cause as well as the strength of the contribution made by any particular cause. For example, there is evidence that development of arteriosclerosis is influenced by genetics, diet, smoking, mineral content of drinking water, and exposure to carbon disulfide and perhaps other occupational chemicals. Among these, genetics is not susceptible to control; the other factors are to varying degrees. Discussed below are a number of prevalent diseases for which there is evidence that environmental chemicals contribute significantly to causation. This is not an exhaustive list. It includes some examples for which environmental chemicals are strongly involved;

others are less strongly associated with chemical causes but are of high incidence in the population so that control of chemical causes would have a significant public health impact.

- o Arteriosclerosis, Ischemic Heart Disease, Cerebrovascular Disease

  According to publications of the National Center for Health Statistics, 5 1/2 million people suffered from them in 1970, with about a million of them unable to carry on work because of the affliction. Almost 270,000 person-years were spent in bed and about 900,000 people died from those conditions during 1970.

- o Hypertension, Hypertensive Heart Disease

  Little is known about the environmental causes of hypertension, though there is some evidence that certain metals are involved. Large quantities of copper ingestion can produce high blood pressure; exposure to cadmium enhances this effect. Chronic toxic damage to the kidney can also cause hypertension. More than 14 million Americans were afflicted by these conditions in 1970 resulting in almost 170,000 person-years in bed.

- o Other Cardiac Conditions

  Cardiomyopathy, that is damage to the heart muscle, can result from drinking beer containing cobalt. Other chronic degenerative changes result from chronic exposure to carbon monoxide. Life-threatening chemically-induced arrhythmias have also been demonstrated in humans and in studies on excessive breathing of flurocarbon aerosol propellants in experimental animals.

- Chronic Bronchitis, Emphysema, Pneumoconiosis

These diseases of the lung are strongly related to environmental exposures to chemicals and dusts. The number of cases in the U.S. in 1970 were 6.5 million, 1.3 million and 126,000 respectively. Chronic bronchitis and emphysema are strongly associated with cigarette smoking but are also associated with air pollution and occupational chemicals. Pneumoconiosis results from exposure to various kinds of dusts, mostly through occupational exposure. This ailment, as well as emphysema can be particularly debilitating and requires a substantial amount of medical care.

- Cirrhosis of the Liver, Acute Liver Necrosis

Many cases of cirrhosis are strongly associated with excess alcohol consumption. Cirrhosis can also be caused by toxic chemicals such as phosphorus and chlorinated hydrocarbons. These same chemicals can cause acute necrosis of the liver. If exposure is sufficiently extensive the patient may die. If not, recovery from the acute episode may be followed by cirrhosis. There were 31,000 deaths from cirrhosis in 1970, though this figure includes cases resulting from injections and other causes in addition to the chemical causes discussed above.

- Degenerative Conditions of the Kidney

A number of chemicals are known to cause renal damage including cadmium, lead, arsenic, ethylene glycol, and mercury. Many other environmental and occupational chemicals probably contribute to decreased renal function and delayed excretion of chemicals that can have harmful effects on other organs. The extent of this problem is unknown.

- Acute and Chronic Pancreatitis, Diabetes Mellitus

Toxic chemicals can destroy either the acinar cells of the pancreas, resulting in pancreatitis, or the islet cells, resulting in diabetes. Chlorothiazide, oral contraceptives, aflatoxin, cobalt, ethanol, carbon tetrachloride, ethionine and peromycin have been shown to be toxic to the acinar cells in man or experimental animals. Sufficient acute damage can be fatal. Lower levels of exposure over long periods of time can cause chronic degeneration of the pancreas which can also be fatal.

Evidence for toxic damage to islet cells is largely experimental. It can be caused by alloxan, streptozotocin and cyprohetadine. These observations suggest that diabetes arising late in life may result from chronic exposure to low levels of toxic chemicals. If so, these have not yet been identified.

- Anemias

Several forms of anemia have been shown to have environmental causes. Aplastic anemia is a critical illness that can be caused by the antibiotic chloramphenicol and other environmental chemicals. Lead causes anemia by interfering with hemoglobin synthesis. Symptoms of sickle-cell anemia are brought on or increased by reduced supply of oxygen.

5. Neurological and Behavioral Toxicology

Organophosphorus pesticides, organic solvents, and inorganic metals are known to have neurotoxic or behavioral effects. Reduced alertness, inappropriate reactions and delays are known effects of occupational exposures to pesticides, mercury and some solvents. Carbon disulfide produces a variety of effects,

including muscle thoraxis. Storage battery workers demonstrate decreased performance on sensory, psychomotor and subjective psychological tests at blood levels below those which are normally associated with toxic effects. Similar changes were found in smelter workers exposed to lead and zinc.

Other problems have been noted in fetal development. It is extraordinarily difficult to measure the cost of this problem, inasmuch as many of the neurological changes are both reversible and minimal. In the absence of significant additional work, we can only say that things like major transplacental exposures to chemicals do occur and that they must have costs associated with them.

6. Environmentally Induced Immunologic Disease

Allergic responses to chemicals or the suppression of natural immunologic reactions result in undesirable health effects. Immunohypersensitization can be life threatening or it may manifest itself in a slight skin irritation. The so-called allergic response, depending on the chemical involved and the individual exposed, involves a large range of diseases, many with unkown origin. Serum sickness, anaphylaxis--like reactions, (after exposure to drugs, pollens), hay fever, asthma, contact dermatitis are all examples of immunologically related diseases.

Immune deficiencies have been recognized only since the use of antibiotics. The cardinal sign of these conditions is greatly increased susceptibility to recurrent infections. Patients with immunologic deficiences formerly died of severe infections long before the underlying deficiency could be detected. Primary immune deficiencies are rare and may be hereditary or acquired. Decreased resistance to infections is the major manifestation of primary antibody deficiency syndromes. Impaired antibody response and a decrease in normal immunoglobulins are associated with various cancers and cancer treatments.

The information base in immunotoxicity research is still in the developmental stage although a good deal of progress has been made in understanding the basic molecular aspects of the immune system. This, combined with the lack of a defined clinical role of environmental immunosuppressive agents, makes risk estimation nearly impossible--and undermines any cost estimations.

Some things, however, are known. Occupational and industrial allergens have been recognized with increasing frequency in recent years. These allergens are commonly inhaled and produce pneumonitis. Even with precautions, from 1-10% of industrial workers exposed to legally permissible concentrations of selected allergens will subsequently develop hypersensitivity reactions resulting in lost work time and decreased productivity. These industrially immunosensitizing chemicals include various synthetic resins, piperzine derivatives, penicillin, soldering fumes, heavy metals salts, industrial dyes and various cosmetic and perfume ingredients.

D. Categorizing the Functional Scientific Components of Solutions

In order to deal with these disease problems in an integrated fashion, some means of systematically classifying research directed at them is needed. Such a system will help allocate resources efficiently and monitor progress toward achievement of objectives.

A variety of classifications can be used to describe the kind of work that is ongoing or needs to be done to meet our objectives. In this section we describe general research categories:

1) Exposure analysis;

2) Laboratory research;

3) Clinical and epidemiological research;

4) Risk assessment research.

In the next section, we define and apply criteria to be used in selecting the most profitable areas for research efforts.

1) Exposure Analysis

This area includes sampling, analytic, monitoring, and predictive methods, and methods to measure total exposure and body burden of chemicals: the identification of pollutants, the sources of exposure, environmental transport and alterations (persistence), human and animal absorption, distribution, metabolism, and excretion (toxicokinetics).

Over a period of decades, as demand increased, sampling, analytic, and monitoring methods have been developed for some specialized uses. Because of the growing number of toxic and hazardous substances which must come under scrutiny and control, and the recognized demand for more effective monitoring of impacts on human beings and their environment, the need for a consistent, regularly updated set of sampling, analytical, and monitoring methods is growing. Reliable techniques that detect toxins at minute concentrations are needed to supplement the conventional sampling devices.

Research in exposure analysis may have wide applicability since regulatory responsibility for a particular compound may be invested in a variety of places, depending upon its sources, uses, routes of exposure, etc.

2) Laboratory Research

This is perhaps the largest single area of work and involves the use of laboratory animals and other techniques to assess toxicity, understand the molecular mechanisms of the induced disease, improve and validate toxicity test procedures, and relate laboratory data to man. It includes important subcategories such as short-term test development, the

development of model ecosystems, interactions between hazardous substances, early indicators of toxicity, and animal models which are more predictive of human risk. Each of these subareas deserves some description.

Current animal testing procedures are time-consuming, expensive, and require highly educated and experienced specialists. Testing of the projected number of potentially toxic substances cannot be accomplished with available facilities, equipment, and personnel. Moreover, present procedures, in spite of their sophistication, suffer continuous criticism within, as well as outside the scientific community.

Encouraging progress is being made in the development of rapid, less expensive, and less time-consuming tests for carcinogenicity and mutagenicity. Among the approaches being developed are tests for mutagenesis in mammalian cells, insects, and microorganisms; identification of damage to DNA or its repair; malignant transformation of cells in cultures; and chemical reactivity of activated chemicals with nucleophiles.

Efforts are needed to develop standardized approaches having known sensitivity, accuracy, reproducibility and predictive value for carcinogenic and mutagenic chemicals including those of medium to low activity. A test which would permit substances to be ranked in terms of toxic potential would be extremely helpful. A validated, defensible, short-term test to establish carcinogenicity would be another valuable contribution that would conserve funds and the talents of the scarce individual experts in these disciplines while protecting the public against significant health hazards.

Short-term tests for other forms of toxicity such as teratogenicity or immunologically related problems are much less developed. New research is needed and shorter term tests should be sought to replace those conventional approaches which are most time-consuming.

Model ecosystems research is concentrated on developing and validating models predictive of adverse effects on aquatic and terrestrial organisms. These models are employed to predict and quantify the impact of various toxic chemical-use patterns on aquatic and terrestrial organisms.

Examples of this research include efforts to associate various physical and chemical properties with bio-accumulation and biomagnification potential. This work leads to ecosystem impact projections based upon amounts and distribution of a toxic substance in the environment.

With these projections decision-makers can decide more intelligently whether to restrict certain uses of a particular compound which would lead to its general introduction into the environment.

Present laboratory procedures are limited to determining responses to exposure to a single test substance. In reality, human beings are often exposed to a number of substances simultaneously and are affected by interactive effects of several chemicals on tissue targets. These interactions may produce additive, synergistic or antagonistic effects. We need to be able to predict the effects of simultaneous exposure to groups of chemicals in order to provide a better scientific base for making regulatory decisions. Data are needed on specific mechanisms of chemical action and on structure-activity relationships in order to predict the result of interactions and the effect of exposure to combinations of chemicals. Research could be conducted both to improve mathematical modeling and also to expand the data base.

Present testing procedures rely, in most instances, upon exposure of laboratory animals to toxins for long periods of time at very high dose rates. The observation period is often the life span of the animal. With a more complete understanding of the physiological, biochemical, and pathological processes involved, one could monitor living, exposed animals continuously and develop useful information for decision-making in a much shorter time frame and at much less expense.

It is necessary to develop new animal test systems that more precisely predict human response to exposure to various substances. Expanded effort is particularly needed in behavioral toxicology and teratology. The former field is in its infancy and much additional effort in the development of techniques, the study of effects of many chemical structures on test systems, and a validation of those systems is needed before human effects can be predicted.

Relatively standardized techniques have been developed for identifying animal teratogens, but there is considerable uncertainty regarding their predictive value for human beings. Additional efforts are needed to determine the roles of anatomic structure of the develping fetus, structure of the placenta, and chemical structure and metabolism of species susceptibility. More work is also needed to look for biochemical and physiological abnormalities that may not be anatomically visible and to study effects of intrauterine exposure to chemicals that may not be apparent in the neonatal period.

Although there is good evidence that nutrition affects the sensitivity of an individual to a number of forms of toxicity, there is insufficient information, to design an optimum diet.

3. Clinical and Epidemiological Approaches

The determination of environmentally induced human disease may be the most important step in attacking many of the disease problems.

Human epidemiologic investigations of chronic, irreversible toxic effects may be hampered by a long latent period between exposure and evidence

of damage. It is difficult to identify a cause of damage among the many substances to which the patients have been exposed over a period of years. This difficulty results in continuing exposure of individuals to harmful substances during the latent period.

We need to develop clinical test methods that can be used to identify chronic toxic hazards long before they have caused disease so that exposure can be minimized. If such tests are to be widely usable, they must use specimens that are readily available. For practical purposes, the sample materials are likely to be limited to blood cells, serum and urine. Controlled clinical exposures will probably continue to be done for some time.

For carcinogenic and mutagenic chemicals, at least, enough knowledge now exists to make the development of such tests seem feasible in the near future. Carcinogenic and mutagenic chemicals do not simply disappear into the body, leaving no trace until years later when a cancer develops or a mutant offspring is born. Chemicals are circulated through the blood stream, metabolized, and partially excreted in the urine, while other metabolities may react with cellular macromolecules, bind to them and induce damage to DNA and to chromosomes. The DNA damage may be partly repaired or may lead to somatic cell mutations. Any one of these phenomena can be the basis of a screening test to identify individuals or population groups being exposed to the harmful chemicals. A small amount of field work has already been done on some of these approaches. For example, workers in factories producing vinyl chloride were found to have an increased number of chromosome abnormalities

in their circulating leukocytes. Also, certain classes of carcinogens have been found to be excreted in the urine relatively unchanged, as glucuronide or sulfate conjugates. These can be reactivated enzymatically and the toxic agent will then produce mutations in bacterial test systems. Heavy cigarette smokers and certain chemical workers have been shown by this procedure to excrete carcinogenic compounds. Although there are many more examples of early and promising work, the total effort in the development of any of these test procedures has been limited.

4. Risk Assessment Research

This combines laboratory and clinical studies to provide a scientifically reasonable estimate of risk.

This research provides the basis for correlating laboratory results with human health risks and environmental impacts. Mathematical models have been developed to extrapolate from high-dose to low-dose effects within a biological test system, but the correlation between animal and human responses rests on more complex biological differences. Currently, these mathematical models, i.e., log-probit, exponential, etc., are utilized in the extrapolation of results observed in chronic animal studies to man. Because of the complex nature of this research, two phases probably need to be considered. The first phase uses existing information and methodologies to establish the most suitable approach to quantifying risks for regulatory purposes. Such interim procedures would define the need, the approach, the areas of uncertainty, the social judgments involved, as well as the legal necessity for regulatory actions. Decision-makers will have to accept a higher level of uncertainty in this interim approach in order to get more uniformity.

A second phase would utilize a different approach. Traditional procedures involve long-term animal studies at maximum tolerated doses, after which mathematical models are directly employed to estimate risk to humans. Such procedures do not consider functional biological differences. The uncertainty levels in these estimates should be refined by using other types of biological data. Many toxicologists now believe that it is essential to explain the kinetics, absorption, distribution, biotransformation, reaction and elimination rates of substances in estimating chemical hazards to man. In the last few years several research groups have been developing scientific data which could form the basis for this approach. With this type of information, scientists could more definitively evaluate intera-species, interspecies, and dose response extrapolations to man. Correlations of species differences and toxicokinetics are essential in estimating potential toxicity, especially in chronic exposure conditions.

Risk assessment should be based upon the dose of biologically active chemicals at the target tissue level in test species and in humans. For chemicals that require metabolic activation to produce adverse biologic effects, the assessment could be based upon the amount of chemical that is transformed in the body rather than the original quanitity ingested.

A sound assessment of risk can only be based on a critical evaluation of all the biological reactions that can be predicted in the exposed population. Recent research developments suggest that this is a very promising area.

E. The Necessity for Choice: Some Criteria for Scientific Action

To this point, we have at least partially described the basic problems of environmental origin, as well as the range of research and development that could be undertaken to begin attacking these problems. The major task now confronting us is sorting through the various possibilities to produce

a program for action that fulfills the highest priority needs of the nation. Various objectives and criteria can be debated in arriving at a final recommendation. Initially, it is crucial we have some scientific assessment that reveals how scientific managers would allocate resources toward the entire set of functional and disease problems in the absence of policy direction and in a system unconstrained by resources This assumes that, even in the best of all possible worlds, not everything would be done at once, but that a certain scientific logic drives the attack on problems.

That scientific logic revolves around the term "researchability". For our purposes, that term has the following components:

1) The strength of the existing data base upon which to build;

2) The ability to do further analysis and experimentation (the "state of the art"); and

3) The size and likelihood of payoff and opportunity cost associated with investment resources.

In Section F, we discuss the relative importance of the disease problems themselves. Here we restrict ourselves to an examination of the scientific criteria to be applied to each of the disease problems. On the basis of this examination and an assessment of the state of "functional" work in each area, we rank the importance of this "functional" work in achieving an understanding and reduction of each social problem.

1. Reproductive and Developmental Toxicity

A. The Existing Data Base

Data exist to help plan and direct future toxic research. Some examples follow. It is known that acute exposure to toxic agricultural chemicals such as dibromochloropropane (DBCP) can cause impotence and infertility in men. Laboratory evidence shows that hundreds of agents are teratogenic in animals--of these 20 to 25 are known to affect humans. Enough information exists concerning normal mammalian male and female reproductive processes to investigate effects caused

by chemical and physical environmental factors. Data exist concerning effects of short-term chemical exposure on mammalian embryos, as well as later stages of development. Pesticide residues are known to occur in human milk, but their effects on nursing offspring are not known. Although it is also known that pathologic and physiologic changes in the user are attributable to the use of oral contraceptives and related pharmacologic agents, it is not known if these changes alter responses to environmental agents in the users and their children. This partial listing of existing data illustrates that the data base is inadequate for understanding all of the problems of reproductive and developmental toxicity, but that the foundations exist for a reasonable research program.

B. Ability to do Further Analysis

Useful existing animal models and experimental procedures can serve as a starting point for further analysis. Much refinement is necessary, however, because current laboratory tests are relatively crude and some biological and chemical procedures are too complex for wide application. Clinical observations also need to be more closely correlated with experimental laboratory findings.

C. Likelihood of Near-Term Payoff

Because of the relatively long time inherent in the process of reproductive maturation and in the development process, near-term payoffs will depend upon success in improving experimental systems, especially those concerned with more rapid and reliable detection of potentially harmful substances and those focusing on early metabolic and biochemical effects on the placental-fetal unit. Increased understanding in these areas could have dramatic effect in protecting the population, particularly pregnant women, from exposure and its consequences.

D. Ranking Importance of Functional Work

On the strength of the available data base, the capability to do further analysis and the dependence of payoff upon the success of improving and refining them both, the highest priority for support is in the area of improving laboratory techniques.

2. Mutagenesis

A. The Existing Data Base

Sufficient scientific data exist to support the identification and planning of further research in mutagenesis. Some examples of ways in which data have been generated and will continue to be developed are the following. Short-term tests provide a battery of techniques which can be applied for screening chemicals and as tools for comparing mutagenicity with other toxic events such as carcinogenicity. In vivo longer term test systems are available to study mechanisms of action and specific mutational events. Chromosomal mutations can be detected in man by cytological techniques. Single dominant gene and recessive gene mutations can be detected using a number of test systems. An automated information system is functioning (Environmental Mutagen Information Center, EMIC) for collecting and disseminating mutagen test information. Current test systems require further evaluation and validation and more data are needed to extrapolate laboratory results to man.

B. Ability to do Further Analysis

In recent years there has been a marked expansion in mutagenesis research with the development of a number of assay systems and a number of non-mammalian and mammalian test systems used for detecting various mutagenic events. A fairly

sound technological base exists for conducting experiments at the molecular level in simple systems which can provide the starting point for more extensive analysis in higher organisms.

C. Likelihood of Near-Term Payoff

Because the data base, although still meager, is sufficient to build upon, and the fundamental technology is developed, the probability of payoff is quite high. Application of recently developed, valuable short-term tests and support from several centers of scientific excellence where genetic research is conducted further strengthen changes of short-term payoff.

D. Ranking Importance of Functional Work

Because there is some ongoing effort in the areas of exposure analysis and laboratory techniques, although insufficient to meet the increasing demands of assessing environmental influences, the necessity to couple clinical with laboratory data runs highest in immediate importance.

3. Carcinogenesis

A. The Existing Data Base

A number of good data bases exist and a large amount of data is available. There are also a large number of experimental techniques available to contribute to the data base and to provide direction for additional research. The magnitude of the problem is such that documentation and information systems need to be expanded to cover the large number of chemicals in more detail and to allow a better in-depth scientific analysis of past and current research. In addition, because some of the existing data were generated prior to the relatively recent development of more sophisticated methods, it is necessary to reevaluate them.

B. Ability to do Further Analysis

Some highly refined analytical methods are available for detecting carcinogens. There are also reasonably good experimental methods for investigating some of the more basic problems. Among them are recently improved techniques for culturing human tissues which can be used to study interactions of carcinogens with human target cells. Bioassay techniques are also more standarized and more useful than before. Because of the scope and complexity of the problem, more analytical capability is needed, but there is sufficient methodology available to support an expanded research program.

C. Probability and Size of Near Term Payoff

Investment in the prevention of environmental cancer has two levels of payoff--a late "disease prevention" payoff, and a rapid "problem prevention" payoff. Obviously, a comprehensive decrease of carcinogenic exposures in the population can have a major impact on cancer rates. In addition, because recognition of a cancer hazard in an environmental situation often leads to a major societal problem, early recognition and control will contribute to a more constructive cooperative effort toward overall health protection. Monies already invested in cancer research, society's great concern, in addition to "the state of the art" and information base, make it likely that the cancer area has a high probability of immediate payoff.

D. Ranking the Importance of Functional Work

On the margin, exposure analysis and laboratory work must be given equal weight, with clinical and epidemiologic work next in line. A different point of view can be considered, however, which says that the

development of alternative technologies based on lower risk for carcinogenic exposure is the most effective approach and should be given the highest priority. We describe this need to render priorities in the carcinogenics area below.

E. Toward Less Hazardous Alternative Technologies

The prevention of environmental cancer in our society is often dependent on the control of hazardous technologies. In many cases, banning or abolishing a given product or technology is not a feasible alternative: the solution to the problem is in comparing technologies and choosing the least hazardous feasible alternative.

The role of Government in this "creative" technological approach to health protection should not be limited to regulation. In many areas an effective policy may be directed toward the development of alternative, less hazardous technologies or may provide the biomedical research resources necessary for developing the scientific basis, the biological model systems and the monitoring techniques needed in an integrated biological technological approach.

Earmarked support for cancer research specifically addressed to these goals can lead to rapid advances in solving specific prolems, and can provide the timely coordination of toxicological research with technological development. Lack of such coordination, can on the other hand, lead to economical and social disasters.

Some examples illustrate these points:

When evidence of carcinogenicity was revealed for some widely used industrial solvents of the halogenated hydrocarbon series, such as carbon tetrachloride, trichloroethylene and chloroform, a number of industrial processes shifted to related

solvents not known then to be carcinogenic. Subsequent findings demonstrated the carcinogenicity of some of these alternative solvents. Regulation that results in the adoption of an alternative product presenting equal or higher hazard than the one being regulated is clearly not in society's interest. In order to avoid pushing the adoption of one "untested techology after the other, only to catch up some time later with further case-by-case regulation, a number of alternative products should be studied simultaneously, not only in terms of usage testing but also in terms of comparative toxicology, including metabolism, tissue retention and excretion, various toxic properties and biological effects. In a relatively short period of time a coordinated research effort should provide a rational approach to the adoption of the safest technology compatible with technical needs. Investment in this research will most likely save major costs caused by inappropriate technological shifts.

Other examples include the design of new products (drugs, pesticides, food additives, fire-retardants, hair dyes, industrial solvents, propellants, fuels, and many others) in which health-directed research is needed in advance to point towards specific technical solutions to toxicological problems.

Some Government supported research has already been addressed to these goals, directly in some cases (such as integrated pest control and development of a less hazardous cigarette) and indirectly through general support to toxicological and biological research.

In this respect we do not envision the need for a large budgetary increase, but rather the focusing of research support to integrate technical and biomedical research projects towards stated problem-solving tasks.

4. Chronic Degenerative Disease

A. The Existing Data Base

These diseases generally result from a complex interaction of genetic susceptibility, nutritional

state, and physical and emotional stresses in addition to specific exposures to various environmental factors. Our knowledge of the organic systems and the way in which they are influenced by these multiple stresses is not now adequate to understand and prevent chronic degenerative diseases. However, there is a sufficient data base relating to the capacity of some organs to metabolize foreign and endogenous substances and some understanding of the effects of species, strain, sex, age, and diet in these processes to provide guidance for setting the direction research should take to begin to solve some of these problems.

B. Ability to do Further Analysis

The essential technological requirements for further analysis are available. Analytic techniques are reasonably well developed, monitoring techniques are available for many compounds and there are some model systems which are satisfactory for investigating single direct toxic effects of organs. However, they are not satisfactory as models for diseases of multifactorial origin such as arteriosclerosis and hypertension. Suitable models that correlate well with human health effects of environmental origin are critically important and still in need of development.

C. Likehood of Near Term Payoff

Payoff will come in degrees because of the complexity of the interactions of many factors. For example, it is known that pollutants of occupational and urban environments may cause or aggravate diseases of the lung. Understanding some aspects of these interactions, as in the case of smoking or exposure to asbestos, should lead to preventive measures for some problems of the lung. The same thing is true

of problems of the gastrointestinal tract, the cardiovascular system, liver, kidney, and hematopoietic system. Stepwise payoff is probably the pattern that will develop for each of the chronic degenerative problems.

D. Ranking Importance of Functional Work

Clinical aspects are the functional area of highest priority. At the present time, chronic disease epidemiology is hampered by the long delay between exposure to a toxic chemical and the development of disease symptoms. During this period, patients also have been exposed to many other agents and sorting out the causative factors is very difficult. This problem is greatly reduced as the time between exposure and measurable effects is reduced. There are now good theoretical reasons to believe that it should be possible to circumvent the problem by developing biochemical and immunologic tests that reveal occurrence of early cellular damage from toxic chemicals long before symptoms develop. If successful, such tests would be used to detect early damage from chemicals or drugs before it is irreversible. This is an area of high payoff that should be given strong encouragement.

5. Neurotoxicity and Behavior

A. The Existing Data Base

There is an adequate data base for planning research in this area. For example, data exist from early animal studies that concentrated on effects of human central nervous system toxicants. There have also been some laboratory studies on the effects of environmental agents and behavioral processes directly in humans. Principles based on data from studies in experimental

behavioral pharmacology can be applied to planning research. Much still needs to be done, however, and concepts and methodologies to investigate subtle neurologic and behavioral effects of environmental agents need to be developed further and expanded.

B. Ability to do Further Analysis

Procedures to support further analysis are reasonably well developed. Neurobehavioral toxicological research, with its foundations in neuropharmacology and experimental psychology, uses test methods that can be applied to detection of health effects. Repeated, chronic exposure to low levels of neurotoxic substances, for example, may produce subtle changes such as reduced alertness, and inappropriate reactions or delays which can be detected by existing neurobehavioral tests. There are also procedures which can be used to evaluate behavioral toxicity in animals and humans. In general, tests currently in use are reasonable sensitive and with further refinement should become more reliable for predicting toxic effects.

C. Likelihood of Near Term Payoff

The sensitivity of some of the present tests and their value as early indicators of exposure to toxic substances, coupled with research already being appled in the field of clinical indicators, create a good potential for short--term and long-term payoff.

D. Ranking Importance of Functional Work

Based on the degree of development of the laboratory techniques and the high potential of the research on clinical indicators, these both rank high in priority because of the possibility for payoff.

6. Immunologic Disease

A. The Existing Data Base

Enough data exist on basic principles of immunology and on immunopathologic mechanisms to serve as a guide for planning research in this area. Useful data also exist on occupational and industrial allergens. There are also useful but limited animal and human data which can serve as a starting point for profitable research in this area. Although a great deal of progress has been made in understanding the basic molecular aspects of the immune system, the information base in immunotoxity is only beginning to be developed. Especially important is the need to expand studies of immunopathologic effects of chronic low-dose exposure to environmental agents.

B. Ability to do Further Analysis

Work done in the field of basic immunology provides a basis for further analysis. However, the area of immunotoxicity is in the developmental stage and needs increased attention. For example although occurrence of immunohypersensitivity is obvious, its etiology is often obscure and predictive laboratory tests are not sufficiently reliable to contribute to understanding cause and effects. Immunosuppressive agents are more easily identified in the laboratory, but is is difficult to document their role in human disease. In short, techniques and scientific manpower are available to investigate the more basic aspects of immunology, but they need to be developed to address the more general problems of immunopathology.

C. Likelihood of Near Term Payoff

Payoff is likely to come in degrees. For example, if sufficient information can be developed about the immunochemical properties of industrial chemicals to provide an indication of potential immunogenicity, it would be possible to minimize worker exposure and help to alleviate an appreciable industrial health hazard.

It is possible that short-term payoff in immunogenicity or allergenicity can be achieved if hazardous chemicals can be identified and more effective measures for protecting workers can be developed even before mechanisms are understood. On the other hand, the problem of immunotoxicity related to environmental agents is more complex from the stand point of preventive medicine. Payoff may be longer term because of the necessity to undertand the interactions and influences of a variety of factors such as intensity and durations of exposure, host genetic factors, coexisting disease states and metabolic aberrations.

C. Ranking Importance of Functional Work

Real progress in understanding and controlling the effects of environmental agents and immune responses depends upon building on existing knowledge to develop more useful and reliable laboratory techniques for predicting immunotoxicity and for distinguishing between immunologic and nonimmunologic adverse reactions to environmental agents. Consequently, development of laboratory techniques is of highest priority.

7. Summarizing the Scientific Criteria

On the basis of this evaluation of the "researchability" of the scientific problems in each disease area, we ranked their importance in allocating resources toward the entire human health effects problem. As we do later with the disease categories themselves, we rejected--as being impossible--a totally quantitative analytic approach. We believe the process of criteria establishment and ranking through which we reached decisions were sufficiently orderly to permit summation. Consequently, we reached the following

ranking--considering only the criterion of "research-ability":

1) "Laboratory Research" (the development of short-term tests, model ecosystems, interactions between hazardous substances, early indicators of toxicity, and more predictive animal models) is still the most critical area. In chronic degenerative diseases, clinical indicators of toxicity and epidemiology are considered sightly more important. In general, however, we believe that the laboratory is still the key to cracking the environmental health problem.

2) Clinical Indicators and Exposure Analysis of toxicity, including epidemiology, in humans, rank very closely behind laboratory tests with animals--and, in some areas, such as chronic disease, and mutagenesis problems--need to be given most weight.

3) As we make progress on the clinical and laboratory fronts, we need to shift our emphasis toward risk assessment. At this time, however, we believe it would be a mistake to escalate risk assessment research over the other areas. Obviously, however, the task of risk assessment must continue to proceed while we cope with more fundamental questions.

This last ranking emphasizes the importance of accelerating action now, so that the decisions of regulatory agencies may soon become founded upon better risk assessment. However, there will be a lag time until that risk assessment work is informed most properly by the basic and applied sciences. We think this point is important because it minimizes the short-term conflict between the needs of regulatory agencies and the research agencies. It is in the regulatory agencies' interest to have an accelerated program in the more fundamental sciences (directed at relevant health end points), so that improved risk assessment can be expected to come on line in the middle range.

It is in the research agencies' interest to have the fruits of their fundamental labors quickly converted into clinical and regulatory knowledge. The ultimate usefulness of the basic sciences can only infuse the research scientists with new energy to pursue their work.

F. Targeting for Action: The Social Problems

In describing the extent of the problem, we emphasized the overall magnitude of environmentally induced disease in our society. We could set this analysis apart, and design research programs based only on the scientific criteria, "researchability", set out above. This would lead to program alternatives and investment in the best scientific apparatus, regardless of their relevance to a particular endpoint or disease.

As money becomes more restricted, and as Research and Development (R & D) increasingly competes with "action" programs for discretionary funds, we think it is necessary to grapple with the problem of targeting. Policy makers and managers must decide which of the disease problems are relatively more important in the society, and pay some attention to this criterion in program design. We fully realize that many research scientists don't plan their own research on the basis of this targeting approach, and our attention to it should not force the individual researcher to alter any given protocol. However, it is meant to serve as guidance to the program manager and policy maker--and will, we think, introduce the necessary creative tension into the system to produce good research.

Addressing the question of importance is uncomfortable, because it means the necessity to make choices. Will the parents of a child with Downs' Syndrome understand if we decide that environmental cancer is more important? Will the cancer patient undertand if we now place more emphasis on chronic disease problems? Probably not. The best we

can do is identify our objective, define criteria to be used in choosing means of achieving that objective, and provide for flexibility to support important breakthroughs in any area.

In the final analysis, we will give considerable weight to questions of scientific researchability: social importance and researchability must influence each other.

1. Objective

Our objective is to minimize the adverse health effects caused by environmental toxins, now and in the future, as efficiently as possible while maintaining the technological progress to which our society is committed.

2. Criteria for Choice

A. The Concept of Marginality

In the economic world, it is axiomatic to make choices with a view to getting the largest possible additional effect with the next unit of resources. Simultaneous activities should be carried to levels where they all yield the same additional return per unit of input. For our purposes, we have translated these concepts into the following question:

> Where will additional research and training dollars in toxicology make the largest incremental impacts on the environmentally based disease problems?

B. Long-run vs. Short-Term: Individual vs Species

Perhaps the most difficult question to face is the one dealing with the proper nature of a public investment in R and D. In one sense, all R and D is future oriented, by the intrinsic nature of foregoing present actions to get future results.

In traditional analysis, these long-term results need to be discounted substantially for the following reason:

> The simple investment of money now at a particular interest rate will produce a stream of benefits into the future. Any research investment must produce at least that stream of benefits (albeit of a different kind) for it to be worth the public's money;

We have this concept into consideration as we considered the nature of the disease problems conflicting us. Cancer, chronic degenerative diseases, immunotoxicity and neurotoxicity can be said to impact primarily in the near term, and to be individual specific. They inflict terrible personal physical costs, and psychological costs on friends and loved ones. Reproductive, and mutagenic problems tend to be longer term in nature--and to have fantastic consequences for the species--not merely additive but multiplicative costs are involved.

Consequently, we are left with competing values: the public investment criteria and the devastating nature of current prominant disease draws us to consider the near-term importance. The potential magnitude of long-run species oriented problems pulls us in that direction.

On the margin, we believe that more attention must be given to problems of the moment, but not to the degree that traditional public investment criteria would drive us. Consequently the problems of reproductive toxicity and mutagenicity receive somewhat more attention here than they might otherwise.

C. Transferring Knowledge to Action - Regulatory Importance

General agreement exists that present Government toxicology programs are subject to conflicting demands. On the one hand, they are pressed to be "relevant" to regulatory agency needs. On the other, they must explore the fundamental boundaries of knowledge so that regulation and other Government action (or inaction) may ultimately be more rational. Health regulation is currently under attack from a variety of corners. We think it is fundamentally important that the weight of the toxicology enterprise be oriented toward rational regulation. This probably means a marginal shift in the direction of near-term regulatory payoff. The important question, of course, remains: How do we allocate resources to achieve that?

3. Ranking the Problems

We applied the criteria suggested above in a subjective fashion. We could have employed some fairly rigorous and quantitative approaches to research ranking. We didn't, primarily because we don't believe that such methods really remove subjectivity from the equation. A member of the task force led discussion around the "importance" of each disease area. Every other member of the panel felt free to comment on the findings and rank and rerank the categories. The task force leader did force conclusions when none seemed to come forth voluntarily. We came to the following conclusions, keeping in mind the three criteria:

1) Expected effects of research--taking account of past investment;

2) Emphasis on present--short-term--individually oriented problems;

3) Emphasis on areas that seem to be of greatest regulatory importance:

- Methods for identifying and controlling the environmental causes of chronic degenerative diseases, such as emphysema, diabetes, and cardiovascular problems need to be the top priority for the near-term future.

- While emphasis on cancer research per se has quadrupled in the past decade, the problems of environmental carcinogenesis are so large--because of the social costs and regulatory laws--that the area must still be given high priority (second only to chronic diseases. We cannot discount the psychological costs of suffering and fear that people derive from this complex of diseases. As we have seen, it may be time for a reordering of priorities in the environmental carcinogenesis area by shifting funds to the development of less hazardous technologies.

- Reproductive disorders and birth defects must take on new importance in light of the state of the art, and the possible magnitude of these problems. In the long run, the costs imposed by this area may be the most important to remedy.

- The problems of neurotoxicity, mutagenic disease and immunologic disease all deserve increased attention as their prevalence becomes known, but research here can be expanded at a somewhat slower rate than the others.

G. The Problem of Training

Toxicology is a deprived and uncertain discipline in this country. No research program in environmental health will succeed unless some attention is paid to the health of the workforce that will run it. The problem is not surprising, in light of the novelty attached to the human health hazards of toxic substances. Even though the number of potentially dangerous substances has increased at an exponential speed as technology has advanced since the end of the second world war, we have only recently begun to assess the health effects of these chemicals. Toxicology involves the application of different disciplines, and consequently the "discipline" of toxicology is murky. Well trained people are hotly competed for, and facilities are limited.

The field of comparative toxicology that will allow extrapolation of test results between whole animal species is not very advanced. Similarly, cellular level work constitutes a new and rapidly developing field. The greatest demand in the field of toxicology is for operational testing and evaluation. Passage of new Federal statutes such as the Resource Recovery and Conservation Act, Consumer Product Safety Act, and the Toxic Substances Control Act (TCSA) has greatly increased the need for toxicologists.

1. Demand in the Discipline

   The TSCA alone is estimated to require over 1,000 toxicologists to be implemented. The increased demand will be in the form of a one time jump followed by a smaller, relatively constant rate of replacement. (Demand in the discipline should level off as shorter-term tests begin to substitute for more labor intensive methods.) The nature of toxicology makes it evident that the most valuable people will be those trained in more than one of the fields.

2. Program Requirements

   We don't believe that it will be necessary to invest heavily in a program to train graduate students in toxicology per se. Rather, the greatest need is to establish top-flight competence in one discipline and then provide funds to permit some cross-training in a related discipline. Many scientists (microbiologists, analytic chemists) and physicians find themselves in less than optimal situations, and are prime candidates for cross-training or retraining, as the situation demands. We believe that this kind of situation provides assurance against the possibility of overtraining that has occurred in some areas in the past.

3. Who Benefits?

   In considering whether to recommend explicit funds for training--not an altogether popular choice--we had to decide whether the benefits to society from such a recommendation would be outweighed by the costs of the program. We realize that some people will ultimately find their place in industry--and that the public will have then borne the burden, while the specific company and individual will reap the benefits. We believe,

however, the benefits of any research effort in environmental health will not fully accrue to society unless an adequate work force is present. Unless that workforce is explicitly planned for and monitored, research money will be siphoned off into training in a way that would not be optimal nor anticipated to train new Ph.D.s. On balance, we believe that training should be provided for explicitly and carefully monitored to ensure that money is used primarily for retraining of available scientifically trained people, not for a massive or diversionary effort to train new graduate students.

4. Establishing a Priority

Rather than looking at training separate from all other subjects, or permitting training to become incorporated as "overhead" for other research activities, we ranked it among with the other "functional research categories". While important to begin, it falls below the other research categories.

H. Policy Alternatives

We have identified our objective, defined criteria for choosing means for achieving that objective and ranked the "functional scientific probems" and the outcome oriented disease problems according to those criteria. We have, in other words, all the components for making a public policy choice in this important area.

A number of reasonable, policy alternatives emerge from our analysis. Each implies a different strategy for allocating resources, and would achieve our objective to a varying extent.

Alternative I: Target new research at the most important disease problems.

Under this approach, the Government would set priorities aimed toward the reduction of disease states, but would permit scientific managers a free choice in allocating the available funds toward those scientific

problems deemed most important. Scientific managers would measure results on the basis of progress toward understanding the direction of particular disease states. Relatively clear "outcome" measures might be developed, and scientists would be held reponsible accordingly.

Pros

- Gives the public and public policy makers the clearest view of progress (or the lack thereof) in the environmental health area.

- Provides scientists and managers with clear incentives.

- Tends to promote an outcome oriented view that may focus efforts.

Cons

- Probably does not conform to the way most scientists view their research problems.

- On a day-to-day basis, makes it difficult to manage the direction of a scientist's effort, since, by definition, all leads toward an end would be pursued.

If this option were accepted, the Government would place its initial new investments on chronic disease problems, second increments on environmental cancer and reproductive problems, and a third increment on mutagenesis, neurotoxicity, and immunologic problems. Stated another way, new money would be placed first on near term payoff problems followed by species oriented longer term investments.

Alternative II: Target new research and training monies on the most important scientific problems, primarily using the "researchability" criteria.

Under this approach, the Government would set priorities along the scientific parameters with little attention to progress toward development of new methods, techniques, etc.--all the things that make a scientific enterprise go. In essence, this would be parallel to the techniques used successfully in basic biomedical sciences, where the decisions have largely been determined--with only loose constraints--by scientists.

Pros

- While imposing some overall dollar limits, which might be quite flexible, the scientists would actually be setting priorities. This would presumably yield the best return on investment from a scientific perspective.

- Mirrors the successful approach in some other areas of the biomedical sciences.

Cons

- Makes it difficult to monitor progress toward societal goals.

- Can result in research endeavors that are difficult to explain to the public in a time of fiscal difficulty.

Under this option, first increments would be directed toward laboratory research, clinical problems and exposure analysis followed by risk assessment and training in additional increments.

Alternative III: Orient all new research and training toward regulatory needs.

A case can be made that exposure analysis and risk assessment of particular chemicals can be brought to the forefront. Regulatory agencies would implicitly have first call on resources allocated to the research institutes.

Pros

- Would definitely meet a perceived need by regulatory agencies and others that research institutions have been unresponsive in the past.

- Might provide some stong near-term payoffs and give a needed "jolt" to the system.

Cons:

- Could destroy the entire research system by pitting research agencies against regulatory agencies.

- Could distort scientific reality by pressing for more work in risk assessment before the scientific underpinning is really available.

- Could lose sight of the health endpoints of the entire enterprise.

Under this option, initial increments would be oriented toward risk assessment, exposure analysis, with laboratory techniques, clinical techniques, and training receiving any other monies.

Alternative IV: Try to allocate resources in such a way to balance:

1) Health endpoints--or objective oriented research;

2) Overall social importance including regulatory needs; and

3) The ability to undertake research.

Under this alternative which, not surprisingly, we recommend, the initial allocation decision would be fundamentally determined by health endpoints and the importance of the social problems. These decisons would be balanced by a realization of "what's possible" and research within disease categories would be balanced accordingly. The needs of regulation are considered as part of the targeting process, but only as one factor in a larger equation that considers other resource, investment and public health factors. Management of this enterprise is more complicated, because it involves the interplay of a number of forces.

Pros

- Permits a balancing of complex social and scientific questions.

- Gives emphasis to regulatory needs without slighting the necessary research.

- Enables policymakers and research managers to monitor progress through identification and subsequent reduction of disease problems. Appropriate indicators would need to be established.

- Gives scientists both sufficient scientific and policy direction.

- Stays away from allocating too specifically. Categories are general enough to permit flexibility, yet sufficient to broach the problem.

- Emphasizes the importance of training without raising it to undue importance.

Cons

- The mingling of various factors makes for more complicated program management.

- Lacks the simplicity of other alternatives and, hence, can be the subject of confusion.

Under this alternative, work on chronic disease (particularly laboratory and clinical work) could receive first priority. Environmental carcinogenesis, with special emphasis on the development of alternative technologies, would come next.

Table I illustrates how funds for a hypothetical program of $200 million would be allocated under this proposal.

I. How Much Should We Spend?

1. Problems with the Base

Many social problems compete for scarce resources. We therefore cannot merely exhort our fellow citizens to spend more money on the important problems of environmental health. We must first prove that more money is needed. This involves, by necessity, an examination of present efforts.

We experienced great difficulty in determining the following:

1) The right subset of all Federal R and D dollars for proper comparison;

2) The best data upon which to establish a base;

3) The amount of overlap and duplication that might exist in current R and D spending.

We looked to the Budget of the U.S. Government for guidance, and found a number of competing data bases. For 1978, the Budget indicated that $493 million would be spent on environmental health research--within a total Federal outlay of $3.5 billion for health research (or roughly 14% of all health research outlays). We then looked to the Special Analysis on the Environment in hopes of verifying this figure. We found nothing exactly comparable, although $320 was cited by the OMB Special Analysis as the 1978 Budget authority for "understanding the effects of the environment on man", and $291.3 million was estimated as 1978 outlay for "research" on environmental impact on man. The latter figure is 14% of all environmental research outlays for FY 1978. We were thus left with a paradox in which two supposedly authoritative data bases conflicted by nearly a factor of 2. At any rate, it was at least clear that the base should be no larger than $500 million. We also assumed that other health and environmental research is not sufficiently fungible to the candidates for short-term reallocation.

We examined a draft report of the Toxic Substances Strategy Committee (Dated July 25, 1978), that report identified approximately $645 million in overall research related to toxic substances in FY 1977--although only $460 million was directly targeted at toxicology. Two areas were of particular interest to us in establishing the proper base for comparison: Human Exposures and Mechanisms for Action. The Report indicated that all agencies combined spent $171.5 million directly on these areas in 1977 and $193 million when highly related research was included.

Based on a recent inventory of toxics research, it has been estimated that $136 million of research of common interest to EPA, FDA, CPSC, and OSHA is currently underway within the Government. We think this probably represents too small a data base for our purposes.

To this point only a piece of the $400 million or so dollars spent on all environmental health research related to toxic substances has been examined. Roughly $70 million has been examined by the Research Planning Group of the Interagency Regulatory Liaison Group. That group found little overlap or duplication in the entire area of *in vivo* (laboratory) toxicology and recommended a doubling in size of this part of the program (+$62.5 million). The Second Task Force on Human Health identified billions of dollars worth of research worth doing.

In the summer of 1978, the Office of Management and Budget conducted a comprehensive "zero-based" review of toxics research. Seven agencies were included: The Food and Drug Administration, the National Institute for Environmental Health Sciences, the National Cancer Institute, and the National Institute for Occupational Safety and Health--all from HEW; the Environmental Protection Agency, the Occupational Safety and Health Administration and the Consumer Product Safety Commission.

This review placed 1979 funding for human health effects research at $400 million. It identified priorities within the base, and began examining questions concerning the appropriate role of basic research in the National Cancer Institute and other important issues. It identified little overlap or duplication among agencies. Results should be available from OMB in January 1979.

2. Conclusions

This discussion leads us to the following conclusions:

- The right base for comparison is between $300 and $450 million dollars; certainly less than 1/2 billion.

- No reliable data base upon which everyone agrees currently exists.

- o No large scale overlap or duplication exists between the research and regulatory agencies, although the regulatory agencies would like research agencies to "be more responsive".

- o More needs exist than can ever be funded with resources that are likely to be available.

3. Cost Estimates

We can undoubtedly expect more definitive studies of the Federal and private data bases. On the basis of the scientific, managerial, and fiscal information we have before us, we believe that a phased program of about $200 million above current spending would be optimal in a non-inflationary budget environment. We believe that a four year increment of $50 million per annum would permit wise allocation but still infuse the environmental health sciences.

Table 1

Allocation of Funds

	"Functional" Research and Training Categories						
	Lab Techniques[1]	Clinical[2]	Exposure[3] Analysis	Risk Assess-ment	Training	Other[4]	Total
Disease Category							
1. Chronic Degenerative Disease	$12.5[5]	$17.5	$10	$5	$4	0	$49
2. Environmental Cancer	8	4	12	2	2	12	40
3. Reproductive Toxicity	12	8	8	8	3	0	39
4. Neurotoxicity and Behavior	9	9	6	3	3	0	30
5. Mutagenic Disease	4	6	8	2	2	0	22
6. Immunologic Disease	6	4	4	4	2	0	20
Total	$51.5 Million	$48.5 Million	$48	$24	$16	$12	$200

1. This includes short-term test development, development ecosystems, interactions between hazardous substances, early indicators of toxicity, and more predictive animal models.

2. Includes epidemiology.

3. Exposure analysis includes sampling and analytic methods, methods to measure total exposure, and body burden of chemicals.

4. Development of alternative technologies to reduce cancer risk.

5. All numbers are expressed in millions of dollars.

APPENDIX I

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